



A miracle of evolution, the human immune system is not controlled by any central organ. . . . Rather it has developed to function as a kind of biologic democracy, wherein the individual members achieve their ends through an information network of awesome scope.

Peter Jaret, 1986

A Simpler Test for Cervical Cancer

Researchers from The Johns Hopkins University in Baltimore, Maryland, and the University of Zimbabwe in Harare have good news for women in developing nations. According to an article published in the 13 March 1999 issue of *The Lancet*, simply wiping the cervix with a solution of acetic acid (vinegar) and visually inspecting the area can reveal more than 75% of precancerous lesions in cervical tissue. The study was conducted by members of the Cervical Cancer Project of the JHPIEGO (pronounced "ja PIE go") Corporation, an affiliate of Johns Hopkins.

During the test, the examiner swabs the cervix with vinegar and then inspects the area with the naked eye. The vinegar causes precancerous tissue to appear as clearly visible white blotches. The study looked at nearly 11,000 African women between the ages of 25 and 55. The study had two parts. In the first part, nearly 9,000 women were examined by trained nurse-midwives at 15 clinics throughout Zimbabwe. The vinegar test and a standard Pap smear were administered at the same time and the results compared. If the vinegar test yielded an abnormal result, the woman underwent colposcopy (which uses a high-powered magnification device to examine the cervix) to confirm the results. In the second part, an additional 2,200 women received both the vinegar test and a Pap smear as well as colposcopy, regardless of whether their screening results were negative or positive. Because all the women in this phase received colposcopy, the JHPIEGO researchers felt the part two results were more valid than those from part one, and so they based their *Lancet* report on the second set of results.

The part two women also received a human papillomavirus (HPV) screening to determine whether an HPV test would be a useful adjunct to the vinegar test. Nearly all cases of cervical cancer are caused by infection with HPV, which is one of the most common sexually transmitted diseases. (These findings will be published at a later date.)

Among the part two women, who received both screening and colposcopy,

the scientists found that the vinegar test correctly designated more women as having disease than the Pap smear did, identifying nearly 77% of abnormal results as compared to just over 44% for the Pap smear. However, specificity (the proportion of nondiseased women who were accurately assessed during screening as being test-negative) in this part was lower for the vinegar test than for the Pap smear. Only 64% of the women who had been identified as test-negative with the vinegar test were confirmed by subsequent colposcopy to not have precancerous lesions, compared to nearly 91% of the nondiseased women who had been identified as test-negative with the Pap smear. Paul Blumenthal, an associate professor of gynecology and obstetrics at Johns



The acid test. When swabbed with an acetic acid solution (vinegar), the healthy cervix looks pink (left). On the diseased cervix, however, precancerous lesions appear as white blotches (right).

Hopkins and a report coauthor, says improved training in properly identifying suspicious blotches—for instance, being able to distinguish them from signs of infection—may reduce the relatively high number of false positives associated with the vinegar test.

Cervical cancer causes some 200,000 deaths in developing nations each year, as compared to about 5,000 deaths per year in the United States. But according to the *Lancet* article, only about 5% of women in developing nations in Africa, Asia, and Latin America are screened for cervical cancer, versus as many as 70% of women in industrialized nations. Pap smear screening—which involves transportation of specimens, technical training of practitioners, and follow-up on negative results—requires a health care infrastructure that many poorer nations currently lack.

According to the American Medical Women's Association, a national organization of women physicians and medical students, cervical cancer is nearly 100%

curable if precancerous lesions are detected in time. According to the *Lancet* article, however, by the time most women in developing nations seek medical help, they are at an advanced stage of cervical cancer.

Blumenthal believes the vinegar test is advantageous for developing nations. The test is simple to perform, inexpensive, and provides nearly instant feedback. The test has been used by gynecologists for at least 40 years, he says. According to Blumenthal, in the United States the test is usually used as a secondary detection measure as part of the colposcopy process. But in developing nations, the test may soon become a first line of defense against cervical cancer.

The article notes that there are costs to both the patient and the health care system involved in false positive results. Blumenthal says JHPIEGO will undertake several medium- to large-scale projects within the next few years that will look at issues of safety, feasibility, and the willingness of local patients and practitioners to accept both the test itself and subsequent immediate treatment. He says, "With a test-and-treat approach, you're going to screen a lot of women who have never been screened before, and most likely you're going to find a lot of disease." The question is whether

local medical infrastructures will be able to support the treatment services necessary for dealing with all the new cases.

The Shape of Hemes to Come

By describing the three-dimensional shape of protein functional groups called hemes, John Shelnett, a member of the technical staff at Sandia National Laboratories and a professor of chemistry at the University of New Mexico in Albuquerque, and his colleagues have opened a new window into the world of molecular biology. Their research suggests a new way to identify the function of many of the molecules most essential to life—molecules that break down pollutants, carry oxygen, sense diatomic molecules, and metabolize drugs and toxicants. Their findings could have important implications for medical science sensor technology and waste remediation techniques.

Hemes serve as the docking and chemical activation sites for other molecules on proteins such as hemoglobin, cytochromes,

JHPIEGO Corporation/Research and Evaluation Office

and many enzymes. Each heme consists of an organic ring called a porphyrin that holds an iron atom in its center. This central iron atom typically bonds to chemicals, attaching them to the protein.

Although all hemes have a similar chemical structure, they play very different and specific roles in proteins. For example, the heme of hemoglobin binds oxygen for transport (and gives hemoglobin its distinctive color), while the heme of cytochrome P450 is involved in metabolizing many drugs and carcinogenic chemicals. Shelnutt's research suggests that the heme's shape is extremely important in determining which biological job a protein does.

The structure of a myoglobin heme protein that stores oxygen in muscle tissue was first discerned by Max Perutz in 1959. Since then, researchers have used X-ray crystallography—the same method employed by Perutz—to map the structure of over 1,000 hemes and model hemes. Researchers have often noticed distortions in the heme but until recently, no one recognized that these structural details could be correlated with the heme's chemistry. Shelnutt and colleagues have used computer analysis to find that the distortions in the heme are conserved from protein to protein and appear to be related to the protein's function. "He's taken all these heme proteins whose structures have been solved, that have widely different functions, and he has, by a very simple algorithm, related all of the distortions in those proteins to one another," says Kenton Rodgers, an associate professor of chemistry at North Dakota State University in Fargo. That is something that no one before Shelnutt realized would be possible.

By analyzing the structures of over 400 proteins in the Brookhaven Protein Data Bank, Shelnutt has found that hemes in proteins are not flat, as was once thought, but instead are bent and warped in very specific ways. In an article in the February 1998 issue of *Biophysical Journal*, Shelnutt described six shape variations, called deformations, that he found to be important for determining the shape of all the hemes he studied. Shelnutt identified these deformations as saddling, doming, ruffling, propeller, and two types of waving. "The neat thing that [Shelnutt] has figured out is that there are only a few types of structural adjustments that nature is able to impose on hemes," explains Rodgers, "but there can be different linear combinations of those structural adjustments." These combinations are characteristic of specific classes of heme proteins.

Shelnutt and his colleagues also found that the magnitudes of these deformations were conserved in many heme proteins with similar functions. In other words, hemes with similar jobs were found to have similar shapes.

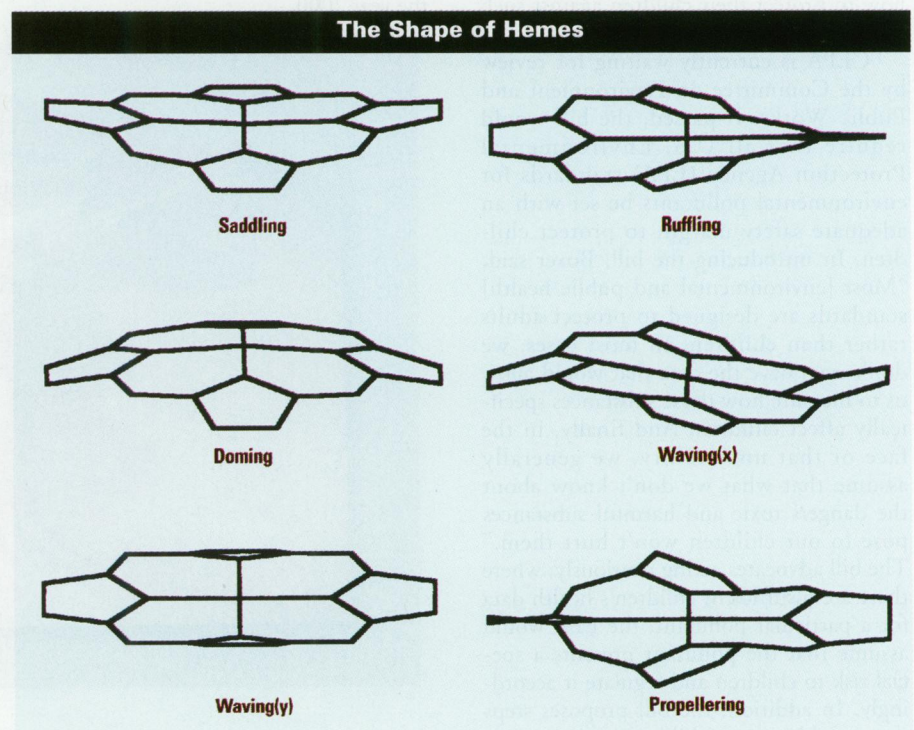
Even some proteins with very different structures but similar functions were found to have matching hemes. This discovery was surprising because the forces exerted by the rest of the protein molecule are what give the heme its shape. However, Shelnutt found that this homogeneity is often the result of a short segment—called the fingerprint peptide—that is attached to the heme. "We show that all the rest of the protein that is wrapped around the heme has a minor influence compared to this little short piece that's attached to the heme itself," he says. However, for other types of proteins, the entire protein brings about the observed shape.

"By looking at all of these hemes in the database," Shelnutt says, "we can correlate the shapes with the function the protein has. But that alone doesn't prove that shape is important in its function. You also need to look at specific heme

organism that carries out nitrogen fixation, to show how the shape of a heme can control a protein's function. In FixL, the shape of the heme changes when the protein binds to oxygen, explains Rodgers, who is studying how oxygen causes such structural changes. The researchers propose that this shape change is propagated throughout the rest of the protein, starting a chain of events that causes the cell to turn off nitrogen fixation. The results of this work were published in the 22 December 1998 issue of *Proceedings of the National Academy of Sciences*.

If the shape of the heme is the primary factor determining the function of a protein, it follows that the function of a protein could be discerned by looking at its heme. Researchers say that this could help isolate the enzyme that metabolizes a certain pollutant or binds a certain drug.

Practical applications of this research are already being developed. For example, Shelnutt and Jean-Pierre Mahy of Université René Descartes in Paris are now looking at the heme of an enzyme called prostaglandin synthase that is involved in triggering inflammation. It is possible that the shape of this heme can be



[proteins] . . . and see if you can show by experiment that the shape is controlling what it does. We've done both of those things now."

Michael Chan, an assistant professor of biochemistry at Ohio State University in Columbus, and his colleagues have used a protein called FixL, which is found in an

used to design new anti-inflammatory drugs that would bind to it. A greater understanding of the hemes of cytochrome P450 may help scientists uncover how this protein selects the molecules that it metabolizes. This could be extremely important in developing anti-cancer drugs because many chemicals only

become carcinogenic when they are acted upon by cytochrome P450.

There is also hope that the structure of hemes can be used to identify the heme-based enzymes that bacteria use to break down common pollutants. These enzymes could then be isolated and used for *in situ* waste remediation. The use of isolated proteins would eliminate the need to use whole bacteria to clean up wastes and thus eliminate problems associated with bacterial overgrowth.

Proposal to Boost Children's Health

In a bid to provide better protection for children's health, U.S. Senators Barbara Boxer (D-California) and Frank Lautenberg (D-New Jersey) introduced the Children's Environmental Protection Act (CEPA), on 24 May 1999. CEPA is an amendment to the Toxic Substances Control Act of 1976 and seeks to protect children from exposures to hazardous substances such as toxic air pollutants and pesticides sprayed in schools. The act would also provide parents with the information necessary to make decisions about how to protect their children against such health threats.

CEPA is currently waiting for review by the Committee on Environment and Public Works. If passed, the bill would require that all U.S. Environmental Protection Agency (EPA) standards for environmental pollutants be set with an adequate safety margin to protect children. In introducing the bill, Boxer said, "Most [environmental and public health] standards are designed to protect adults rather than children. In most cases, we don't even have the data that would allow us to measure how those substances specifically affect children. And finally, in the face of that uncertainty, we generally assume that what we don't know about the dangers toxic and harmful substances pose to our children won't hurt them." The bill advocates acting cautiously; where there are insufficient children's health data for a particular pollutant, the EPA would assume that the pollutant presents a special risk to children and regulate it accordingly. In addition, the bill proposes steps that would protect children against pesticide use in schools, including the development of a list of the most toxic pesticides (such as developmental toxicants and known or suspected carcinogens) that would be distributed to all schools and day-care centers. Two years after enactment of CEPA, schools and day-care centers would be prohibited from using the

New Global Environmental Reporting Prize

The World Conservation Union (IUCN) announced on 5 August 1999 that an international jury will select the winner of a new global prize for excellence in environmental reporting. The first annual Reuters-IUCN Media Award will be presented by Reuters Foundation and the IUCN to honor one print journalist with an opportunity to study at Oxford University for three months. The award will cover tuition, travel, and accommodation expenses.

Reuters Foundation was established in 1982 as an educational trust to promote high standards in journalism study and training. The IUCN is the world's largest conservation-related organization and was created in 1948. Reuters Foundation and the IUCN established the awards to challenge journalists to raise the standard in environmental coverage.

"The jury will be looking for high-quality environmental reporting based on sound scientific data," said foundation director Stephen Somerville in an IUCN press release. "We want to encourage lively, responsible journalism that can make a difference, that alerts and informs both the public and the policy makers."

Regional winners will be selected by regional juries, but the global winner will be selected by a panel of conservationists and journalists. The six jurors include Queen Noor of Jordan, a patron of the IUCN; Yolanda Kakabadse, president of the IUCN; Kader Asmal, chairman of the World Commission on Dams and South Africa's minister of education; Maurice Strong, chairman of the Earth Council and rector of the United Nations University of Peace; Geoffrey Lean, a leading British journalist; and David Rogers, chief news editor at Reuters.

"Conservationists need to share their knowledge with the media while journalists have to link environmental stories with mainstream issues that affect people's lives," said Queen Noor at the IUCN's fiftieth-anniversary celebration in France last November. The winner of the Reuters-IUCN Media Award will be selected in November 1999.

Reuters Foundation and the IUCN are also collaborating to develop a program that will join experts and the media for environmental journalism workshops and symposia in the year 2000.



listed pesticides. In addition, parents would receive advance notification of in-school pesticide use.

The bill would direct the EPA to review existing standards to ensure they protect children, and to complete revisions of any standards within 15 years. The Children's Health Protection Advisory

Committee, made up of pediatricians, educators, and representatives from the community, nonprofit health organizations, industry, and state health agencies, would assist in this process by providing annual recommendations to the EPA on standards that should be reevaluated. (This committee has already been created